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Papers

Residential and occupational exposure to sunlight and mortality from non-Hodgkin's lymphoma: composite (threefold) case-control study

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Abstract

Objective: To determine whether non-Hodgkin's lymphoma mortality is associated with sunlight exposure.
Design: Three case-control studies based on death certificates of non-Hodgkin's lymphoma, melanoma, and skin cancer mortality examining associations with potential sunlight exposure from residence and occupation.
Setting: 24 states in the United States.
Subjects: All cases were deaths from non-Hodgkin's lymphoma, melanoma, and non-melanotic skin cancer between 1984 and 1991. Two age, sex, and race frequency matched controls per case were selected from non-cancer deaths.
Main outcome measures: Odds ratios for non-Hodgkin's lymphoma, melanoma, and skin cancer from residential and occupational sunlight exposure adjusted for age, sex, race, socioeconomic status, and farming occupation.
Results: Non-Hodgkin's lymphoma mortality was not positively associated with sunlight exposure based on residence. Both melanoma and skin cancer were positively associated with residential sunlight exposure. Adjusted odds ratios for residing in states with the highest sunlight exposure were 0.83 (95% confidence interval 0.81 to 0.86) for non-Hodgkin's lymphoma, 1.12 (1.06 to 1.19) for melanoma, and 1.30 (1.18 to 1.43) for skin cancer. In addition, non-Hodgkin's lymphoma mortality was not positively associated with occupational sunlight exposure (odds ratio 0.88; 0.81 to 0.96). Skin cancer was slightly

positively associated with occupational sunlight exposure (1.14; 0.96 to 1.36).
Conclusions: Unlike skin cancer and to some extent melanoma, non-Hodgkin's lymphoma mortality was not positively associated with exposure to sunlight. The findings do not therefore support the hypothesis that sunlight exposure contributes to the rising rates of non-Hodgkin's lymphoma.

Key messages

- The incidence of non-Hodgkin's lymphoma has risen rapidly in recent decades throughout much of the world
- Several investigators have hypothesised that increased exposure to sunlight may contribute to this rising incidence
- A study in the United States found that sunlight exposure based on residence and occupation was not positively associated with non-Hodgkin's lymphoma
- The study found no evidence to support the hypothesis that sunlight contributes to the rising rates of non-Hodgkin's lymphoma

Introduction

Incidence and death rates for non-Hodgkin's lymphoma have risen rapidly in recent decades throughout the world.[1] Neither changes in diagnostic practices nor known and suspected risk factors seem to account fully for the increases.[2] Several investigators have hypothesised that increased exposure to sunlight may have contributed to the rising rates of non-Hodgkin's lymphoma.[3 4 5 6 7 8] They note that melanoma and other skin cancer rates have also risen rapidly worldwide,[4] that non-Hodgkin's lymphoma and skin cancer are associated in individual patients,[4 6] and that ultraviolet stimulation is experimentally immunosuppressive.[3 7] Ecological studies that have explored this hypothesis have had conflicting results.[3 7 8 9] None, however, examined sources of sunlight exposure other than residence.

We conducted a population based case-control study of non-Hodgkin's lymphoma mortality in the United States. As an improvement over ecological studies, we assessed potential sunlight exposure from both the occupational and the residential records on the death certificate. The findings for non-Hodgkin's lymphoma were compared with findings for melanoma and non-melanotic skin cancer, two diseases regarded as causally linked to sunlight exposure.[10]

Methods

Since 1984 the American National Cancer Institute and the National Institute for Occupational Safety and Health have supported the creation of a 24 state mortality database, which includes coding of occupation and other information from death certificates, as described by Figgs *et al.*[11] Cases included all deaths between 1984 and 1991 from non-Hodgkin's lymphoma (International Classification of Diseases, ninth revision (ICD-9), codes 200 and 202 (excluding 202.2-202.6)), melanoma (code 172), and non-melanotic skin cancer (codes 173, 154.3, and 187.7) in people aged 20 or over identified as white or African American. Two controls per case were selected from non-cancer deaths in the database and matched for frequency by sex, race, and five year age group.

Potential sunlight exposure was assessed by residence and usual occupation recorded on the death certificate. The annual mean daily solar radiation (which includes ultraviolet and visible light) for the state of residence at death and state at birth were obtained from United States Weather Bureau data.[12] Each state was characterised at one of three levels based on the predominant solar radiation contour crossing the state. The 24 states reflected all regions of the country (see table 1).

Table 1 Characteristics of non-Hodgkin's lymphoma, melanoma, and non-melanotic skin cancer cases and controls.† Data expressed as numbers (percentages) of subjects

Occupations were classified by an industrial hygienist (MD) into four categories: indoor work, work that combined indoor and outdoor exposure, outdoor work by non-farmers, and farming. Farmers were categorised separately because some studies have suggested that farmers may be at increased risk of non-Hodgkin's lymphoma due to exposure to pesticides, a potential confounder for which we could not otherwise control.[13] Occupation was also used to create an index of socioeconomic status, with five levels based on a method of scoring devised by Green.[14] Homemakers, retirees, and students were not assigned a socioeconomic level but were controlled for separately. Cases and controls with no identified occupation on the death certificate (about 4%) were excluded from analysis.

The multivariate model included age, sex, race, residential sunlight exposure, occupational sunlight exposure, and socioeconomic status for the entire population, and was analysed by race and sex groups and by age (<45 years, ≥45 years). Birthplace, which was highly correlated with residence at death, was excluded from the model. The effects of skin pigmentation were assessed by classifying subjects based on national origin and race as recorded on the death certificate.

The measure of association was the mortality odds ratio and 95% confidence interval derived by standard logistic regression methods in SAS.[15]

Results

Table 1 gives the numbers of cases and controls for non-Hodgkin's lymphoma, melanoma, and non-melanotic skin cancer deaths by age, sex, race, skin pigmentation,

Table 1 Characteristics of non-Hodgkin's lymphoma, melanoma, and non-melanotic skin cancer cases and controls.† Data expressed as numbers (percentages) of subjects

	Non-Hodgkin's lymphoma		**Melanoma**		**Skin cancer**	
	Cases (n=33 407; 34%)	**Controls (n=65 843; 66%)**	**Cases (n=12 156; 34%)**	**Controls (n=23 845; 66%)**	**Cases (n=4619; 33%)**	**Controls (n=9170; 67%)**
Age (years):						
20-44	2 320 (7)	4 413 (7)	2 290 (19)	4 361 (18)	270 (6)	526 (6)
45-54	2 587 (8)	4 994 (8)	1 753 (14)	3 378 (14)	401 (9)	798 (9)
55-64	5 646 (17)	11 089 (17)	2 405 (20)	4 742 (20)	912 (20)	1803 (20)
65-74	9 885 (30)	19 590 (30)	2 753 (23)	5 474 (23)	1163 (25)	2302 (25)
≥75	12 969 (39)	25 757 (39)	2 955 (24)	5 890 (25)	1873 (41)	3741 (41)
Sex:						
Female	16 609 (50)	32 822 (50)	4 900 (40)	9 590 (40)	1566 (34)	3125 (34)
Male	16 798 (50)	33 021 (50)	7 256 (60)	14 255 (60)	3053 (66)	6045 (66)
Race:						
Black	1 818 (5)	3 535 (5)	208 (2)	400 (2)	410 (9)	810 (9)
White	31 589 (95)	62 308 (95)	11 948 (98)	23 445 (98)	4209 (91)	8360 (91)
Pigmentation:						
Fair‡	1 806 (5)	3 782 (6)	691 (6)	1 346 (6)	232 (5)	500 (5)
Other white	29 783 (89)	58 526 (89)	11 252 (93)	22 099 (93)	3977 (86)	7860 (86)
Black	1 818 (5)	3 535 (5)	208 (2)	400 (2)	410 (9)	810 (9)
Residence§:						
Low sun	11 553 (35)	21 244 (32)	3 646 (30)	7 613 (32)	1330 (29)	2972 (32)

Moderate sun	13 529 (41)	26 334 (40)	4 792 (39)	9 384 (39)	1839 (40)	3692 (40)
High sun	8 325 (25)	18 265 (28)	3 718 (31)	6 848 (29)	1450 (31)	2506 (27)
Birthplace‖						
Low sun	11 000 (33)	20 496 (31)	3 797 (31)	7 626 (32)	1252 (27)	2757 (30)
Moderate sun	14 290 (14)	27 861 (42)	5 135 (42)	10 023 (42)	2007 (43)	3885 (42)
High sun	6 863 (21)	15 245 (23)	2 870 (24)	5 478 (23)	1218 (26)	2147 (23)
Occupation:						
Indoor	17 054 (51)	31 125 (47)	6 574 (54)	11 734 (49)	2225 (48)	4393 (48)
Mixed	14 081 (42)	29 502 (45)	4 723 (39)	10 166 (43)	1849 (40)	3793 (41)
Outdoor (non-farmer)	867 (3)	2 302 (4)	406 (3)	993 (4)	250 (5)	441 (5)
Farmer	1 405 (4)	2 914 (4)	453 (4)	952 (4)	295 (6)	543 (6)
Socioeconomic status¶:						
1 Low	3 653 (11)	8 917 (14)	1 263 (10)	3 151 (13)	799 (17)	1530 (17)
2	4 889 (15)	11 055 (17)	1 774 (15)	4 497 (19)	821 (18)	1715 (19)
3	9 771 (29)	17 815 (27)	3 910 (32)	7 015 (29)	1320 (29)	2612 (28)
4	5 177 (15)	8 001 (12)	2 153 (18)	3 245 (14)	575 (12)	1148 (13)
5 High	1 449 (4)	1 954 (3)	754 (6)	878 (4)	187 (4)	311 (3)

†Ratio of controls to cases was slightly less than 2.0 owing to exclusion of subjects with no occupational information.
‡Subjects were characterised as fair skinned if they were white and their national origins were identified as British, Irish, German, Scandinavian, Polish, or other northern European.
§Levels of sun exposure were categorised based on annual mean daily solar radiation reported by Garland *et al*[12] for state reported as residence at time of death. This was sometimes outside the 24 states in which deaths occurred. "Low" included the following states and other areas: Alaska, Connecticut, *Maine*, Massachusetts, Michigan, Minnesota, *New Hampshire*, New York, *Ohio*, Oregon, Pennsylvania, *Rhode Island, Vermont, Washington, Wisconsin,* Canada. "Moderate" included Arkansas, Delaware, District of Columbia, *Idaho*, Illinois, *Indiana*, Iowa, *Kansas, Kentucky*, Maryland, *Missouri*, Montana, *Nebraska, New Jersey, North Carolina*, North Dakota, South Carolina, *Tennessee*, Virginia, and *West Virginia*. "High" included Alabama, Arizona, California, *Colorado*, Florida, *Georgia*, Hawaii, Louisiana, Mississippi, *Nevada, New Mexico, Oklahoma, South Carolina*, Texas, *Utah*, Wyoming, Puerto Rico, Virgin Islands, Guam, Cuba, and Mexico. (States in bold are the 24 states from

the mortality database.)

‖ Levels of sun exposure were categorised as above for state identified as state of birth. Cumulative percentage is less than 100 because birthplace could not be identified in a few cases and controls.

¶Cumulative percentage is less than 100 because socioeconomic status could not be identified for retirees, homemakers, and students.

residence, birthplace, occupational category, and socioeconomic status. Roughly a quarter to one third of subjects lived in states with the highest levels of sunlight. Around 3-5% had outdoor non-farming jobs.

Table 2) gives the odds ratios for non-Hodgkin's lymphoma, melanoma, and non-melanotic skin cancer mortality adjusted for age, sex, race, residence, occupational sunlight exposure, and socioeconomic status. For non-Hodgkin's lymphoma the adjusted odds ratios declined significantly with increasing exposure to sunlight based on residence and occupational category. In contrast, the adjusted odds ratios for melanoma and skin cancer and residential exposure increased, the risk of skin cancer rising significantly to 1.30 among subjects who resided in states with the highest sunlight exposure.

Table 2 Odds ratios (95% confidence intervals) for non-Hodgkin's lymphoma, melanoma, and non-melanotic skin cancer mortality associated with indicators of sunlight exposure and socioeconomic status, adjusted for age, sex, race, and other factors†

The risk of non-farming occupational sunlight exposure for skin cancer was slightly but not significantly raised in outdoor workers (odds ratio 1.14; table 2). In melanoma, however, there was no apparent pattern for non-farming occupational sunlight exposure. Farmers were at significantly increased risk compared with indoor workers for non-Hodgkin's lymphoma and melanoma but not skin cancer. Socioeconomic status increased the association with non-Hodgkin's lymphoma and melanoma but generally not with skin cancer. Similar results were obtained in the crude analysis, with the exception of the odds ratio for farming; this was significantly decreased for non-Hodgkin's lymphoma and melanoma.

The negative residential associations identified for non-Hodgkin's lymphoma in the total population were also seen in the multivariate model in the sex, race, and age subpopulations. The deficit of non-Hodgkin's lymphoma risk associated with residential sunlight exposure was most pronounced in subjects aged 44 years or less (highest versus lowest sunlight region: odds ratio 0.69; 95% confidence interval 0.61 to 0.79). The odds ratio for occupational exposure among men reflected that of the total population. Among women the odds ratios were raised, though not significantly so.

The risk of melanoma and skin cancer increased with residential exposure among white people and subjects aged over 44. No pattern was evident for African Americans. There was also no clear pattern for melanoma or skin cancer risk associated with occupational exposure across the sex, race, or age groups, except that risk of skin cancer increased among subjects aged over 44.

Increased potential sunlight exposure was associated with declining non-Hodgkin's lymphoma risk in each residential area and for each occupational category, the greatest decline occurring among outdoor workers in areas receiving the most sunlight (table 3). The effect was strongest in younger people, among whom the odds ratio declined to 0.44 (0.28 to 0.67) in subjects in occupations and states with the highest sunlight exposure. The risks for skin cancer generally increased with potential residential or

Table 2 Odds ratios (95% confidence intervals) for non-Hodgkin's lymphoma, melanoma, and non-melanotic skin cancer mortality associated with indicators of sunlight exposure and socioeconomic status, adjusted for age, sex, race, and other factors†

	Non-Hodgkin's lymphoma	**Melanoma**	**Skin cancer**
Residence‡:			
Low sun	1.0	1.0	1.0
Moderate sun	0.95 (0.92 to 0.98)	1.08 (1.02 to 1.13)	1.12 (1.02 to 1.22)
High sun	0.83 (0.81 to 0.86)	1.12 (1.06 to 1.19)	1.30 (1.18 to 1.43)
Occupation:			
Indoor	1.0	1.0	1.0
Mixed	0.95 (0.91 to 0.99)	0.92 (0.87 to 0.98)	0.95 (0.85 to 1.05)
Outdoor (non-farmer)	0.88 (0.81 to 0.96)	0.99 (0.87 to 1.12)	1.14 (0.96 to 1.36)
Farmer	1.31 (1.21 to 1.42)	1.31 (1.14 to 1.52)	1.08 (0.89 to 1.31)
Socioeconomic status:			
1 Low	1.0	1.0	1.0
2	1.21 (1.13 to 1.28)	1.11 (1.00 to 1.23)	0.97 (0.84 to 1.12)
3	1.49 (1.40 to 1.57)	1.55 (1.41 to 1.71)	1.03 (0.90 to 1.18)
4	1.73 (1.62 to 1.84)	1.81 (1.63 to 2.00)	1.01 (0.86 to 1.18)
5 High	2.02 (1.86 to 2.20)	2.39 (2.10 to 2.72)	1.22 (0.98 to 1.52)

† Odds ratios were calculated from logistic regression, adjusted for age (categorised as in table 1), sex, race, residence, occupational sun exposure, and socioeconomic status.
‡ See table 1.

occupational sunlight exposure. With melanoma, however, the risk from residential exposure did not increase among outdoor workers; nor did the risk increase with occupational sun exposure, except among subjects with low residential exposure.

Table 3 Odds ratios (95% confidence intervals) for non-Hodgkin's lymphoma, melanoma, and non-melanotic skin cancer mortality by occupational sunlight exposure and residential sunlight exposure, adjusted for age, sex, race, socioeconomic status, and farming status†

Odds ratios for non-Hodgkin's lymphoma increased with skin pigmentation from 1.0 among subjects with northern European ancestry to 1.10 (1.04 to 1.17) among other white groups and 1.26 (1.16 to 1.37) among African Americans. There was no significant association with melanoma or skin cancer. Among subjects with fair pigmentation the odds ratio for non-Hodgkin's lymphoma in the highest sunlight region was 0.92 (0.80 to 1.06). In this group the risks associated with this exposure were raised for melanoma (odds ratio 1.44; 1.15 to 1.79) and skin cancer (1.56; 1.06 to 2.29).

Discussion

This study found no evidence of an excess risk of non-Hodgkin's lymphoma mortality associated with potential sunlight exposure. The results generally showed decreased risk among people with the heaviest exposure. Though the methods used were crude, they produced associations between sunlight exposure and the risk of melanoma and skin cancer mortality. Most other research on non-Hodgkin's lymphoma and sunlight has been limited to ecological data with exposure potential determined by residence alone. This analytical study improved exposure ascertainment by using individual data on occupation, state of birth, socioeconomic status, skin pigmentation, and residence.

Associations with exposure to sunlight

The incidence of skin cancer is thought to be directly associated with cumulative sun exposure.[10 16] Generally, studies of skin cancer incidence and total sun exposure have found associations with odds ratios between 1.2 and 11.0.[17] Consistent with this, we found positive associations between skin cancer mortality and residential and occupational surrogates for exposure to sunlight exposure. In contrast, melanoma was not as closely associated with our indicators of sunlight exposure. The relation of melanoma to sunlight, however, is more complex, with age of exposure[3 10] and intermittent intense exposure[10 18 20] thought to have a role. Studies of melanoma incidence and residential or overall sun exposure have reported significant associations with odds ratios or relative risk ratios of about 1.7.[16 18] In this study residential sunlight exposure at the times of death and birth was associated with melanoma.

Occupational sunlight exposure, however, was not associated with melanoma. The absence of an overall occupational association seems to reflect varied occupational associations among residential regions. In

Table 3 Odds ratios (95% confidence intervals) for non-Hodgkin's lymphoma, melanoma, and non-melanotic skin cancer mortality by occupational sunlight exposure and residential sunlight exposure, adjusted for age, sex, race, socioeconomic status, and farming status†

	Residence‡		
Occupational exposure	**Low sun**	**Moderate sun**	**High sun**
Non-Hodgkin's lymphoma			
Indoor	1.0	1.0 (0.96 to 1.04)	0.86 (0.82 to 0.90)
Outdoor (non-farmer)	0.89 (0.77 to 1.03)	0.87 (0.76 to 0.99)	0.74 (0.64 to 0.86)
Melanoma			
Indoor	1.0	1.10 (1.03 to 1.19)	1.18 (1.09 to 1.27)
Outdoor (non-farmer)	1.22 (0.99 to 1.50)	1.05 (0.86 to 1.29)	0.96 (0.76 to 1.20)
Skin cancer			
Indoor	1.0	1.06 (0.94 to 1.19)	1.28 (1.12 to 1.46)
Outdoor (non-farmer)	0.98 (0.71 to 1.34)	1.42 (1.08 to 1.84)	1.36 (1.01 to 1.83)

† Odds ratios were calculated from logistic regression; adjustments for age were based on age categories in table 1.
‡ See table 1.

both the moderate and high sunlight regions outdoor work was associated with lower risk than indoor work, which might be expected if melanoma is more a function of intermittent exposure than continuous exposure. Occupational studies of melanoma risk and outdoor exposure present divergent findings, studies indicating no association with outdoor work[19] or that outdoor work may protect against melanoma.[18 20]

In marked contrast with the associations with melanoma and skin cancer, we found that both residential and occupational sunlight exposure were inversely associated with non-Hodgkin's lymphoma and that these negative associations characterised most of the sex, race, and age subpopulations. Moreover, risk declined consistently across residential exposure categories as occupational exposure increased and across occupational categories as residential exposure increased. This was true even when the exposure might be intermittent, as in the case of indoor workers living in high sunlight exposure areas.

The stronger negative association with sunlight exposure among younger people further argues against a positive causal role for sunlight exposure in non-Hodgkin's lymphoma. In younger people there is less likely to be misclassification of exposure because occupations and residences recorded at death are less commonly succeeded by a retirement period or preceded by a retirement move.

In support of the hypothesis that sunlight contributes to the incidence of non-Hodgkin's lymphoma, Adami cited the observed increased risk of non-Hodgkin's lymphoma in outdoor workers.[21] Particular outdoor occupations, including farming, forestry, and fishing, have been associated with increased risk of non-Hodgkin's lymphoma.[22] We examined the collective risk of about 40 outdoor jobs other than farming, as well as farming, an occupational exposure that potentially posed particular risks. Our results showed a negative association for outdoor work generally whereas, as expected, the odds ratio for farming was raised.

Other findings in our study supported an association between sunlight exposure and skin cancer and melanoma but not non-Hodgkin's lymphoma. Both melanoma[23 24] and skin cancer[10] have been associated with fair skin. If sunlight plays a part in non-Hodgkin's lymphoma skin pigmentation may similarly affect susceptibility. Thus the lower incidence of non-Hodgkin's lymphoma among African Americans has been cited as supporting the sunlight-non-Hodgkin's lymphoma hypothesis.[21] The reported lower incidence in African Americans in the United States, however, derives from cancer registry data and is not adjusted for socioeconomic status.[25] When we controlled for socioeconomic status the risks in African Americans exceeded those in people likely to have fair pigmentation and other white subjects. Moreover, there was no association between non-Hodgkin's lymphoma and residential sunlight exposure among people with fair pigmentation. In contrast, residential sunlight exposure was strongly associated with skin cancer and melanoma in this group.

Assessing exposure

There were limitations in the assessments of exposure in this study. Characterisation of residential sunlight exposure is subject to many sources of potential misclassification bias. Solar radiation contours were based on data from weather stations that could not measure all places and all conditions. The usual occupation entered on a death certificate may reflect most recent occupation, not a lifetime occupational history. Furthermore, residential exposure was based on state of residence at death, not lifetime residential history. None the less, depending on the region, between about 70% and 80% of subjects were born in the same exposure regions that they resided in at death. Moreover, to the extent that such misclassifications are made non-differentially the resulting bias is likely to dilute associations. This suggests that the true association with non-Hodgkin's lymphoma could be a greater deficit than observed here.

Socioeconomic and cultural differences

Socioeconomic status based on usual occupation at the time of death also could not account for lifetime occupational histories, education, or income. Yet the associations observed with socioeconomic status support the validity of the classification system. Socioeconomic status as categorised in this model showed a dose-response relation with the risk of melanoma, which is consistent with the findings of several studies.[24 26 27] Socioeconomic status also seemed related to non-Hodgkin's lymphoma risk in our study, an association noted in some but not all populations.[25]

We considered the possibility that cultural differences between states in the northern and southern latitudes of the United States would increase the HIV related non-Hodgkin's lymphoma mortality in the north and thus confound observed associations. That we did not include death certificates from California, New York, Florida, or Texas—four states with the highest percentage of AIDS cases[28]—limits substantially potential confounding by HIV related non-Hodgkin's lymphoma mortality. Moreover, such confounding if present would not seem to account for the negative association between residential sunlight and non-Hodgkin's lymphoma in view of the fact that the negative association also characterised the subpopulations of white men, white women, black men, black women, young people, and old people.

The associations explored in this study between sunlight indicators and non-Hodgkin's lymphoma were virtually all negative. That they did not resemble the associations observed between sunlight and melanoma, and particularly sunlight and non-melanotic skin cancer, argues against sunlight as a strong explanatory factor in the increased incidence of non-Hodgkin's lymphoma. This analysis cannot, however, rule out a complex role for sunlight in the aetiology of non-Hodgkin's lymphoma. There may, for example, be unsuspected environmental agents that are both correlated with northern latitudes of the United States and potent causal agents for non-Hodgkin's lymphoma and which mask a positive but weaker association with sunlight. It is possible that such factors are correlated with different latitudes in different countries, thus explaining the varied findings of ecological studies of latitude and non-Hodgkin's lymphoma.[7 8 9] Our finding that indoor work and regions of low sunlight exposure increase, not decrease, the risks of non-Hodgkin's lymphoma needs to be confirmed, and the elusive agent or agents accounting for this increase need to be identified.

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